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Prediction of Arrhythmic Events in Patients Following Myocardial Infarction

T. R. CRIPPS, D.M., M.R.C.P., A.J. CAMM, M.D., F.R.C.P., F.A.C.C.*

National Heart Hospital, and *Department of Cardiological Sciences, St. George's Hospital Medical School, London, England

Summary: The value of techniques used to predict arrhythmic events (sudden cardiac death not preceded by reinfarction and spontaneous sustained ventricular tachycardia) after acute myocardial infarction is reviewed. A full clinical assessment allows the detection of patients with major infarction, present in the majority of those suffering arrhythmic events during follow-up. More sophisticated noninvasive tests, including Holter monitoring, and the high gain, signal averaged ECG, add prognostic accuracy to clinical assessment in patients with major infarction but are by themselves nonspecific. Noninvasive assessment of autonomic function from baroreceptor sensitivity analysis and heart rate variability measurement may also provide useful prognostic information. The results of programmed ventricular stimulation studies in patients with recent acute infarction have been contradictory, though many of the disagreements can be explained by methodological differences. At best this technique is highly invasive, and probably adds little to what can be discovered from a thorough noninvasive assessment. The treatment to be adopted in those judged to be at high risk remains to be established; and this may include nonpharmacological modalities such as the implantable defibrillator and surgical ablation as alternatives to drug therapy.

Key words: myocardial infarction, arrhythmias, electrical stimulation, sudden death

Introduction

Mortality in the first year after acute myocardial infarction is about 10%, and there is a continuing mortality in subsequent years of about 4% per year.[1] Many of these deaths are sudden, unexpected, and thought to be due to ventricular tachyarrhythmias.[2]

In recent years, a number of tests have been applied to postinfarction patients in an effort to identify more accurately those at risk of sudden death. The purpose of this review is to consider how valuable such procedures may be and how they relate to clinical assessment in the prediction of arrhythmic death after infarction.

Clinical Assessment in the Prediction of Arrhythmic Death

Usually, patients who develop spontaneous symptomatic sustained ventricular tachyarrhythmias following distant myocardial infarction have a substantial amount of ventricular damage. Thus, in one study, 35 of 40 patients (88%) with previous infarction investigated for ventricular tachyarrhythmias had an ejection fraction of $<40\%$.[3]

Clinical features indicative of major infarction might therefore be expected to predict late arrhythmic death. Such factors include a history of previous infarction or dyspnea, cardiogenic shock or pulmonary edema, a persistent tachycardia, and elevation of the blood urea concentration.

However, it is common experience that not all patients with large infarcts die during medium term follow-up, so there is still scope for prognostic stratification within the high-risk group, perhaps by differentiating between those with inert myocardial scar tissue and an electrically abnormal region which may provide the substrate for late-phase arrhythmias.

That clinical indicators relating to infarct size are related to long-term prognosis has been recognized for many years;[4-6] it follows that a reduced ejection fraction is also correlated with increased mortality. In the Multicenter Postinfarction Group (MPRG) study, for example, the two-year all-cause mortality in those with an ejection fraction of $<30\%$ was 31%, compared with 7.5% in those with an ejection fraction of $>30\%$. Multivariate analysis showed that ejection fraction contributed independent prognostic information over a number of other individual clinical variables and test results.[7]

Address for reprints:

T. R. Cripps, M.A., M.R.C.P.
Clinical Lecturer
National Heart Hospital
London, England

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However, a later report from the MPRG[8] showed that if all the clinical data available at the time of discharge were taken into account, knowledge of the ejection fraction provided a negligible increase in the sensitivity and specificity of prediction of serious events during follow-up (including cardiac death and nonfatal reinfarction).

Similar results were reported in Madsen's study.[9] Death within 1 year was related to age, previous infarction, displaced apex beat, maximum heart rate, blood urea concentration, and early reinfarction, but ejection fraction was not an independent predictive variable.

Doubt remains, therefore, whether measurement of ejection fraction really adds to a careful clinical assessment in judging prognosis after infarction. The sensitivity and accuracy of the information provided is also insufficient. In MPRG, the sensitivity of an ejection fraction <40% for predicting all-cause mortality (the proportion of patients who died who had an ejection fraction <40%) was only 60% (55/91) and the positive predictive accuracy (the proportion of patients with an ejection fraction <40% who actually died) was only 20% (55/271). Even dichotomizing the results at an ejection fraction of 30% resulted in a predictive accuracy of only 31% (39/124).[7]

Thus, while major infarction is one important factor in the genesis of late mortality, measurement of ejection fraction does not provide all the necessary information required to predict this event satisfactorily.

High-Gain Signal-Averaged ECG

One of the most interesting developments in the noninvasive prediction of arrhythmias in recent years has been the development of the high-gain, signal-averaged ECG.[16] Low amplitude potentials arising from areas of delayed myocardial activation are detected using a high-gain, body surface ECG, with signal averaging added to improve the signal to noise ratio so that potentials in the microvolt range can be detected. Devices which carry out this process at the bedside with little more trouble than is required to perform a standard 12-lead ECG are now available.

Several postinfarction studies[17-21] have now been published (Table I). The sensitivity of the technique seems quite high, in the 70–90% range for arrhythmic events, though the predictive accuracy is still low ($\approx$ 20%).

Several fundamental limitations restrict the technique. The interpretation of the results in patients with bundle-branch block and atrial fibrillation remains in doubt. In some patients the volume of the myocardial tissue participating in the re-entrant circuit is too small to produce body surface potentials of sufficient amplitude; in some, there is a varying coupling interval with the main QRS complex so that temporal signal averaging is ineffective. Furthermore, not all patients with an area of conduction delay develop manifest sustained arrhythmias. Finally, in some patients, a terminal arrhythmia arises as the result of a change in the electrophysiological properties of the myocardium (perhaps as a result of reinfarction).

TABLE I Summary of the results of prognostic studies involving the high gain, signal averaged electrocardiogram in patients with recent acute myocardial infarction

Reference	Author	No.	Time since MI	LP+ (%)	Follow-up	Device	Sensitivity	Specificity	PPA	Comments
17	Breithardt *et al.* 1983	160	7-109 (median 3.2 mo)	51	7.5±3.2 mo	Dusseldorf	73	51	10	Q wave MI only
18	Denniss *et al.*, 1986	306	7-28 days	26	2 years	Uther	66	78	24	Q wave only; PVS also
19	Kuchar *et al.*, 1987	200	7-40 days (11±6)	39	6 mo-2 years	ART (40 Hz)	93	65	17[a]	
							65	89	31[b]	
							80	89	34[c]	
20	Gomes *et al.*, 1989	115	10±6 days	42	4±8 mo	ART (40 Hz)	81	65	27	Holter and EF also performed
21	Cripps *et al.*, 1988	159	3±2 days	24	12±6 mo	ART (25 Hz)	91	81	26[a]	
							73	97	62[b]	

[a]Late potentials only.

[b]Late potentials and frequent ectopics.

[c]Late potentials and reduced ejection fraction.

Abbreviations: LP+, late potentials present; MI, myocardial infarction; PVS, programmed ventricular stimulation; PPA, positive predictive accuracy.

Nevertheless, the technique is rapid, totally noninvasive, and relatively inexpensive and shows promise, particularly if other prognostic information is taken into account when interpreting the results (see below).

Programmed Ventricular Stimulation

The application of programmed ventricular stimulation to the postinfarction patient remains highly controversial. In view of the relatively invasive nature of the technique, the skill involved, and its high cost, it would indeed be alarming if it was shown that every postinfarction patient should be evaluated electrophysiologically.

The results of a number of the published studies are shown in Table II. They fall into two groups: those which seem to show that the technique is highly sensitive, if fairly inaccurate,[22-27] and those that are inconclusive or appear to deny any value for the technique.[28-31]

Greene's original study[22] relied on the induction of repetitive responses, which have subsequently been shown to be unreliable indicators of those with a propensity to sustained ventricular tachycardia. That of Marchlinski *et al.*[28] was insufficiently sensitive as a screening test, employing as it did only double extrastimuli. Bhandari's group[29] focused on a low-risk group, and allowed antiarrhythmic drugs to be given to some of those with inducible, sustained arrhythmias. The studies of Roy[30] and Santarelli[31] and their co-workers were limited in the few endpoint events.

The studies which provide the most positive results are those of Hamer,[23] Richards,[24] Waspe,[25] Breithardt,[26] and ourselves[27]. Common features include an aggressive stimulation protocol, with up to three extrastimuli, the definition of a positive response as sustained monomorphic ventricular tachycardia, and a complete follow-up without systematic antiarrhythmic therapy.

Under these circumstances, the test seems fairly sensitive (70–100%) but not sufficiently accurate (40–70%), bearing in mind its invasive nature (25% of our patients required DC cardioversion during the test). It has also been our experience that information as accurate can be obtained using a combination of noninvasive criteria, though the stimulation study may still have a place in the selection of therapy in patients so judged to be at risk of arrhythmic death.

Combinations of Tests

Several authors have examined the value of the combination of high-gain, signal-averaged electrocardiography, Holter monitoring, and ejection fraction measurement in postinfarction patients. The combination has theoretical appeal, since the ejection fraction might select a high-risk group with major infarction, the high-gain, signal-averaged ECG, the substrate for arrhythmias within the area of infarction, and, on Holter, the occurrence of spontaneous arrhythmic activity.

TABLE II Summary of the results of prognostic studies using programmed ventricular stimulation to predict arrhythmic events in patients with recent myocardial infarction

Reference	Author	No.	Time since MI (days)	Positive response	Follow-up (mos.)	Sensitivity	Specificity	PPA	Comments
22	Greene *et al.*, 1978	48	8-85 (24)	2+VEs	12	79	86	79	1 extra stimulus; 2 RV sites
23	Hamer *et al.*, 1982	37	7-20	5+VEs	12	80	75	33	2 extra stimuli; 2 RV sites
24	Richards *et al.*, 1983	165	7-28 (10)	VT/F>10 s	(8)	91	30	18	High voltage stimulation included
25	Waspe *et al.*, 1985	50	7-36 (16)	7+VEs	(23)	100	77	41	3 extra stimuli; 2 RV sites
26	Breithardt *et al.*, 1986	132	<6 weeks	4+VEs	(15)	77	57	16	2 extra stimuli
27	Cripps *et al.*, 1989	75	(21)	SMVT	median 16	100	97	75	3 extra stimuli
28	Marchlinski *et al.*, 1983	46	8-60 (22)	4+VEs	(18)	17	78	10	2 extra stimuli; 1 RV site
29	Bhandari *et al.*, 1985	45	9-21 (14)	VT/F	(10)	Insufficient events			Low-risk patients
30	Roy *et al.*, 1985	150	8-20 (14)	6+VEs	(10)	Insufficient events			
31	Santarelli *et al.*, 1985	50	17-40 (25)	10+VEs	4-16	Insufficient events			

Abbreviations: RV, right ventricle; PPA, positive predictive accuracy; SMVT, sustained monomorphic ventricular tachycardia; VEs, ventricular extrasystoles; VT/F, ventricular tachycardia or fibrillation.

The results show that these tests do appear to provide independent predictive information for arrhythmic events after infarction.

Thus, in the study of Kuchar *et al.*,[19] all three tests were independent predictors of arrhythmic events. The occurrence of both late potentials and frequent ectopics was 65% sensitive and 89% specific for arrhythmic events; the occurrence of late potentials and a reduced ejection fraction was 80% sensitive and 89% specific.

Gomes *et al.*[20] also found an independent relationship between these three variables: patients with a reduced ejection fraction, frequent ectopics and late potentials had an event rate of 50%, while no patient with a negative result in all tests had an arrhythmic event.

In our own study,[21] we found that the combination of late potentials and frequent ectopics in a patient with any clinical complications during the in-hospital phase was associated with a very high risk: 8 of 9 such patients had an arrhythmic event during follow-up.

Detection of Abnormalities of the Autonomic Nervous System

The importance of the autonomic nervous system in the genesis of cardiac arrhythmias has long been appreciated.[32] Assessment of baroreceptor sensitivity to detect a sympathovagal imbalance[33] in survivors of infarction, which might facilitate fatal arrhythmias, has recently been carried out by Schwarz *et al.*[34] Baroreceptor sensitivity, a primarily vagal function which may be swamped by excessive sympathetic discharge, was markedly reduced in four patients who suffered sudden death out of 78 who underwent baroreceptor testing after infarction.

Holter Monitoring to Predict Arrhythmias After Infarction

The ability to record and rapidly analyze long periods of electrocardiographic activity was applied to the postinfarction patient[10] in the hope that a tendency to dangerous arrhythmias could be detected, and then prevented by antiarrhythmic therapy. Unfortunately, the reality is far from this ideal.

In the Multicenter Investigation of the Limitation of Infarct Size study (MILIS), the occurrence of ventricular ectopics more frequent than 10/h was predictive of sudden death during a mean of 18 months follow-up in 533 patients who survived to 10 days after infarction.[11] The predictive value of frequent ectopics was independent of a reduced ejection fraction. Other authors have reported similar results.[12-14]

However, when the results of Holter monitoring were considered in the context of all the clinical information available at the time the tape was recorded, the information provided gave no increase in the accuracy of prediction of either all-cause mortality[9,15] or the occurrence of cardiac death and reinfarction at 1 year.[8]

The nature of the endpoints chosen in these studies, however, deserves comment. Cardiac death includes death from fatal arrhythmias, reinfarction, and other causes not related to the occurrence of arrhythmias. When assessing the value of a test designed to predict arrhythmias, it is preferable at least to use sudden death as the endpoint, and probably to include the occurrence of spontaneous sustained ventricular tachycardia.

In the study of Tibbitts *et al.*,[8] for example, Holter monitoring would not be expected to predict reinfarction, nor is it clear why nonfatal reinfarction was included as an endpoint, but sustained ventricular tachycardia was not.

Nevertheless, an overview of the postinfarction Holter studies must leave some doubt as to whether the detection of nonsustained arrhythmias on Holter monitoring really adds to clinical assessment in postinfarction patients.

Although there was no clear relationship between baroreceptor sensitivity and left ventricular ejection fraction, doubt has been expressed as to whether this test provides information which is independent from that already available from other sources.[35]

Another technique relating to assessment of autonomic tone in postinfarction patients is analysis of heart rate variability. Increased sympathetic activity, which may facilitate the occurrence of arrhythmias, is associated with a fall in heart rate variability and an increase in mean heart rate.

Kleiger *et al.*[36] found that reduced heart rate variability was more powerful than any of the other Holter variables, including ectopic frequency, in predicting all-cause mortality after infarction. The prognostic value of reduced heart rate variability appeared to be independent of a reduced ejection fraction.

The prognostic value of such techniques, in relation to other prognostic variables, remains to be established, but our preliminary results[37] suggest that heart rate variability analysis is indeed a very powerful method for predicting mortality and arrhythmias in postinfarction patients.

Conclusion

It is clear that clinical assessment has a great deal to offer in the prediction of arrhythmias following myocardial infarction. It is unusual for a patient with a completely uncomplicated clinical course to suffer an arrhythmic event: one suspects that in such cases there has been a change in the electrophysiological milieu, probably as the result of a new ischemic event.

Within the high-risk group defined by the presence of clinical evidence of major infarction, perhaps supported by a reduced ejection fraction, however, the presence of complex ectopic activity and late potentials defines a subgroup at even greater risk.

The value of antiarrhythmic measures in such patients remains to be proved, but it is now possible to identify postinfarction patients with a risk of arrhythmic events of 50–90%, and in these patients a systematic trial of antiarrhythmic therapy is now required.

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